HFA-305, Division of Docket Management

Date of Approval: AUG 13 2003

FREEDOM OF INFORMATION SUMMARY

Abbreviated New Animal Drug Application

ANADA 200-338

TRI-HEART Plus (ivermectin/pyrantel) Chewable Tablets

For the prevention of canine heartworm (*Dirofilaria immitis*) disease and for the treatment and control of adult *Toxocara canis*, *Toxascaris leonina*, *Ancylostoma caninum*, *Uncinaria stenocephala*, and *Ancylostoma braziliense*.

Sponsor:

Heska Corporation
1825 Sharp Point Drive
Fort Collins, Colorado 80525

FOIS

1. GENERAL INFORMATION:

a.	File Number:	ANADA 200-338
b.	Sponsor:	Heska Corporation 1825 Sharp Point Drive Fort Collins, Colorado 80525 Drug Labeler Code: 063604
c.	Established Name:	Ivermectin/Pyrantel
d.	Proprietary Name:	TRI-HEART Plus (ivermectin/pyrantel) Chewable Tablets
e.	Dosage Form:	Chewable tablet
f.	How supplied:	TRI-HEART Plus is supplied in 3 dosage strengths for dogs of different weights. Each strength comes in packs of 6 chewable tablets.
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	Small tablet contains 68 mcg of ivermectin and 57 mg pyrantel (as pamoate salt); medium tablet contains 136 mcg of ivermectin and 114 mg pyrantel (as pamoate salt); large tablet contains 272 mcg of ivermectin and 227 mg pyrantel (as pamoate salt).
i.	Route of Administration:	Oral
j.	Species/class:	Canine
k.	Recommended Dosage:	A minimum of 6 mcg of ivermectin and 5 mg of pyrantel (as the pamoate salt)/kg of body weight at monthly intervals.
l.	Pharmacological Category:	parasiticide/anthelmintic

m. Indications:	Prevents heartworm disease by eliminating the tissue stage of heartworm (*Dirofilaria immitis*) larvae for a month after infection and for the treatment and control of ascarids (*Toxocara canis, Toxascaris leonina*) and hookworms (*Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense*).
n. Pioneer Product:	HEARTGARD Plus (ivermectin/pyrantel) Chewables, Merial Ltd., NADA 140-971.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product).

A Suitability Petition (98P-0927/CP1), requested by Heska Corporation, was granted to allow a generic copy of the pioneer's extruded chewable tablet with this compressed chewable tablet. The different dosage forms are similar and can be used interchangeably.

The sponsor has demonstrated *in vivo* bioequivalence, via clinical endpoint bioequivalence studies, of the generic product to the pioneer product to support the safety and efficacy of the generic product against *Dirofilaria immitis* (see Section 2.a.) and *Toxocara canis* (see Section 2.b.). Palatability was also evaluated in dogs and the study is reported below in Section 2.c.

The use of clinical endpoint bioequivalence studies instead of blood level bioequivalence for the ivermectin component was based on the fact that accurate measurement of blood levels was not possible for ivermectin at the approved dose over the entire pharmacokinetic profile.

The use of clinical endpoint bioequivalence studies for the pyrantel (as the pamoate salt) component is based on the poor absorption of pyrantel from the digestive tract, where it is locally active, and the poor correlation between blood levels and effectiveness.

a. Clinical Endpoint Bioequivalence for Canine Heartworm Disease Prevention

Two clinical endpoint bioequivalence studies were conducted against *Dirofilaria immitis* at the same facility, with the same objectives, and the same basic study design, but on different dates. The first study was invalidated due to inadequate infections in the control animals. The second study is described below.

Testing Facility: Professional Laboratory & Research Services, Inc.
Corapeake, North Carolina

Objective: The objective of this study was to determine the comparative efficacy of TRI-HEART Plus (ivermectin/pyrantel) chewable tablets and HEARTGARD Plus (ivermectin/pyrantel) chewables against developing stages of heartworm (*Dirofilaria immitis*) in dogs. *Dirofilaria immitis* was selected for testing because it is the parasite species on the pioneer product label which is eliminated by the ivermectin portion of this anthelmintic combination (ivermectin/pyrantel) product.

Design: Thirty beagle dogs (9 males, 21 females) ranging from approximately 8 to 10 months of age, and weighing between 17.5 and 25 pounds were artificially infected (*D. immitis* L3 larvae), ranked by weight within each sex, and randomly assigned to one of three treatment groups containing 7 females and 3 males. The dogs were treated 29 days after infection with TRI-HEART Plus chewable tablets (Group 2) or the pioneer product, HEARTGARD Plus chewables, (Group 3) at the recommended dosages. The negative control group (Group 1) received no treatment. The dogs were observed daily until sacrifice and necropsy 182 to 189 days post-infection. At necropsy, the heart and connecting vasculature of each dog were removed and the heartworms located in these organs were counted.

Results:

Table 1.

Group	Treatment	Geometric Mean Worm Count	Range	Percent Efficacy
1	None	48.2	37-60	N/A[1]
2	TRI-HEART Plus	0	N/A	100
3	HEARTGARD Plus	0	N/A	100

[1]N/A- not applicable

Percent efficacy was calculated using the following formula:

[(Geometric mean # of worms recovered from control dogs)-(Geometric mean # of worms recovered from treated dogs)]/(Geometric mean # of worms recovered from control dogs) x 100 = % efficacy

The generic product and the pioneer product were both 100% effective against developing stages of heartworms in dogs and no further statistical analysis was conducted.

Conclusion: The test product, TRI-HEART Plus Chewable Tablets, was found to be bioequivalent to the Reference Product, HEARTGARD Plus Chewables, with respect to claims for effectiveness in the prevention of infection with *Dirofilaria immitis*.

b. Clinical Endpoint Bioequivalence for Control of Gastrointestinal Nematodes

Testing Facility: Professional Laboratory & Research Services, Inc.
Corapeake, North Carolina

Objective: The objective of this study was to evaluate the comparative efficacy of Heska's TRI-HEART Plus (ivermectin/pyrantel) chewable tablets to that of Merial's HEARTGARD Plus (ivermectin/pyrantel) chewables for the treatment of adult roundworms (*Toxocara canis*) in dogs. *Toxocara canis* was selected for testing because it is the canine parasite species on the pioneer product label most resistant to the effects of pyrantel pamoate.

Design: Thirty puppies, naturally infected with *T. canis* (12 males, 18 females), of various breeds were enrolled in the study. The puppies were approximately 6 weeks of age or older, and weighed between 2.6 and 19.0 pounds at treatment. Weight ranked puppies were randomly assigned to one of three treatment groups of 10 puppies, each containing male and female pups, with the proportion of each sex dependent on body weight. Dogs receiving the generic product (Group 2) and the pioneer product (Group 3) were administered a single dose at the recommended dosage. The negative control group (Group 1) received no treatment. All dogs were observed daily until necropsy 7 days after treatment at which time the gastrointestinal tract of each dog was removed and carefully examined to collect and count all *T. canis* worms.

Results:

Table 2.

Group	Treatment	Geometric Mean Worm Count	Range	Percent Efficacy
1	None	11.9	2-30	N/A[1]
2	TRI-HEART Plus	0.9	0-6	92.4
3	HEARTGARD Plus	0.3	0-7	97.5

[1]N/A- not applicable

Percent efficacy was calculated using the following formula:

[(Geometric mean # of worms recovered from control dogs)-(Geometric mean # of worms recovered from treated dogs)]/(Geometric mean # of worms recovered from control dogs) x 100 = % efficacy.

Both generic and pioneer products resulted in a significant ($P<0.05$) reduction in roundworms compared to controls. Because both treatments resulted in greater than 90% efficacy, no further statistical analysis was undertaken.

Conclusion: The generic product, TRI-HEART Plus Chewable Tablets, was found to be bioequivalent to the pioneer product, HEARTGARD Plus Chewables, with respect to claims for effectiveness against *T. canis* in the canine.

c. **Palatability of Chewable Tablets**

Testing Facility: Summit Ridge Farms
Susquahanna, PA

Objective: The objective of this study was to compare the palatability of TRI-HEART Plus (ivermectin/pyrantel) chewable tablets to the palatability of the pioneer product, HEARTGARD Plus (ivermectin/pyrantel) chewables.

Design: A two-day crossover study was conducted with fifty adult beagle dogs (14 male and 36 female) ranging in age from approximately 1.5 to 7.5 years and weighing between 21 and 47 pounds. Dogs were ranked by body weight within each sex and randomly assigned to one of two treatment groups of 25 dogs each. Group 1 received one TRI-HEART Plus chewable tablet on the first day and one HEARTGARD Plus chewable on the second day. Group 2 received one HEARTGARD Plus chewable on the first day and one TRI-HEART Plus chewable tablet on the second day. The dogs were administered the treatments per label directions. Each dog was offered each treatment in a bowl placed on the cage floor and, after 2 minutes, the treatment was recorded as Consumed, Partially Consumed, or Not Consumed.

Results: Of the 50 dogs enrolled in the study, 45 readily consumed both products. One dog did not accept either product. Two dogs ate the HEARTGARD Plus chewable but did not eat the Tri-Heart Plus chewable tablet. Two dogs ate the TRI-HEART Plus chewable tablet but did not eat the HEARTGARD Plus chewable. McNemar's test showed no statistical difference in palatability between the generic and pioneer product ($P > 0.05$).

Conclusions: TRI-HEART Plus (ivermectin/pyrantel) chewable tablets and HEARTGARD Plus (ivermectin/pyrantel) chewables were found to be equally palatable to dogs.

3. HUMAN SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this ANADA.

Human Warnings are provided on the package label as follows:

Keep this and all drugs out of the reach of children. In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that TRI-HEART Plus Chewable Tablets, when used under the proposed conditions of use, is safe and effective for its labeled indications.

Safety and effectiveness for this generic animal drug, TRI-HEART Plus Chewable Tablets, were established by the demonstration of clinical end-point bioequivalence to the pioneer product, HEARTGARD Plus Chewables, NADA 140-971, sponsored by Merial, Ltd., for the parasites: *Dirofilaria immitis* and *Toxocara canis*. Palatability was also tested and found to be equivalent to that of the pioneer product.

5. ATTACHMENTS:

a. Generic Labeling:

Package Insert
Carton labels:
6 chewable tablets- Dogs up to 25 lbs.
6 chewable tablets- Dogs 26 to 59 lbs.
6 chewable tablets- Dogs 51 to 100 lbs.
Display units of 14 packs of 6 chewable tablets- Dogs up to 25 lbs.
Display units of 14 packs of 6 chewable tablets- Dogs 26 to 50 lbs.
Display units of 14 packs of 6 chewable tablets- Dogs 51 to 100 lbs.

b. Pioneer Labeling:

Package Insert
Carton label

Tri-Heart™ Plus

(ivermectin/pyrantel)

Chewable Tablets

Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS: For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of ascarids (*Toxocara canis, Toxascaris leonina*) and hookworms (*Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense*).

DOSAGE: Tri-Heart™ Plus ivermectin/pyrantel chewable tablets should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of ascarids and hookworms is as follows:

Dog Weight	Chewable Tablets per Month	Ivermectin Content	Pyrantel Content	Color Coding on Foil Backing and Carton
Up to 25 lbs	1	68 mcg	57 mg	Blue
26 to 50 lbs	1	136 mcg	114 mg	Green
51 to 100 lbs	1	272 mcg	227 mg	Brown

Tri-Heart Plus ivermectin/pyrantel chewable tablets are recommended for dogs 6 weeks of age and older. For dogs over 100 lbs, use the appropriate combination of these tablets.

ADMINISTRATION: Remove only one chewable tablet at a time from the blister card. Because most dogs find Tri-Heart Plus chewable tablets palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dry food or placed in the back of the dog's mouth for forced swallowing.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

Tri-Heart Plus chewable tablets should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of Tri-Heart Plus chewable tablets must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the chewable tablet must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with Tri-Heart Plus chewable tablets and resumption of the recommended dosing regimen minimizes the opportunity for the development of adult heartworms.

Monthly treatment with Tri-Heart Plus chewable tablets also provides effective treatment and control of ascarids (*T. canis, T. leonina*) and hookworms (*A. caninum, U. stenocephala, A. braziliense*). Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

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EFFICACY: Tri-Heart™ Plus chewable tablets given orally using the recommended dose and regimen, are effective against the tissue larval stage of *D. immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage. Tri-Heart Plus chewable tablets are also effective against canine ascarids (*T. canis, T. leonina*) and hookworms (*A. caninum. U. stenocephala, A. braziliense*).

ACCEPTABILITY: In acceptability trials, Tri-Heart Plus chewable tablets were shown to be a palatable oral dosage form that was consumed at first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with Tri-Heart Plus chewable tablets which are not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with Tri-Heart Plus chewable tablets.

While some microfilariae may be killed by the ivermectin in Tri-Heart Plus chewable tablets at the recommended dose level, Tri-Heart Plus chewable tablets are not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Keep this and all drugs out of the reach of children. In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Store at controlled room temperature of 59-86° F (15-30° C). Protect product from light.

ADVERSE REACTIONS: In clinical field trials with ivermectin/pyrantel, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of ivermectin at the recommended dose: depression/ lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

SAFETY: Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level of 6 mcg/kg) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. Ivermectin demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies support the safety of ivermectin products in dogs, including Collies, when used as recommended.

Ivermectin/pyrantel has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with ivermectin/pyrantel in a heartworm disease preventive program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

HOW SUPPLIED: Tri-Heart Plus chewable tablets are available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient packs of 6 chewable tablets.

For customer assistance, please contact Heska Corporation at 1-800-464-3752.

Marketed by:
Heska Corporation
1613 Prospect Parkway Fort Collins, CO 80525, USA
Made in USA

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Heartgard® Plus
(ivermectin/pyrantel)
Chewables

Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS: For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae *(Dirofilaria immitis)* for a month (30 days) after infection and for the treatment and control of ascarids *(Toxocara canis, Toxascaris leonina)* and hookworms *(Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense)*.

DOSAGE: HEARTGARD® Plus should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of ascarids and hookworms is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Pyrantel Content	Color Coding on Foil Backing and Carton
Up to 25 lb	1	68 mcg	57 mg	Blue
26 to 50 lb	1	136 mcg	114 mg	Green
51 to 100 lb	1	272 mcg	227 mg	Brown

HEARTGARD Plus is recommended for dogs 6 weeks of age and older.
For dogs over 100 lb use the appropriate combination of these chewables.

ADMINISTRATION: Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to its box to protect the product from light. Because most dogs find HEARTGARD Plus palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dog food. The chewable should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

HEARTGARD Plus should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of HEARTGARD Plus must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with HEARTGARD Plus and resumption of the recommended dosing regimen minimizes the opportunity for the development of adult heartworms.

Monthly treatment with HEARTGARD Plus also provides effective treatment and control of ascarids *(T. canis, T. leonina)* and hookworms *(A. caninum, U. stenocephala, A. braziliense)*. Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

HEARTGARD is a registered trademark and Dog & Hand logo is a trademark of Merial.

EFFICACY: HEARTGARD® Plus (ivermectin/pyrantel) Chewables, given orally using the recommended dose and regimen, are effective against the tissue larval stage of *D immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage. HEARTGARD Plus Chewables are also effective against canine ascarids *(T. canis, T. leonina)* and hookworms *(A. caninum, U. stenocephala, A. braziliense)*.

ACCEPTABILITY: In acceptability and field trials, HEARTGARD Plus was shown to be an acceptable oral dosage form that was consumed at first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with HEARTGARD Plus which is not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with HEARTGARD Plus.

While some microfilariae may be killed by the ivermectin in HEARTGARD Plus at the recommended dose level, HEARTGARD Plus is not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Keep this and all drugs out of the reach of children. In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Store at controlled room temperature of 59°-86°F (15°-30°C). Protect product from light.

ADVERSE REACTIONS: In clinical field trials with HEARTGARD Plus, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of HEARTGARD: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

SAFETY: HEARTGARD Plus has been shown to be bioequivalent to HEARTGARD, with respect to the bioavailability of ivermectin. The dose regimens of HEARTGARD Plus and HEARTGARD are the same with regard to ivermectin (6 mcg/kg). Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. HEARTGARD demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies, support the safety of HEARTGARD products in dogs, including Collies, when used as recommended.

HEARTGARD Plus has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with HEARTGARD Plus in a heartworm disease preventive program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

HOW SUPPLIED: HEARTGARD Plus is available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 6 and 12 chewables.

For customer assistance, please contact Merial at 1-888-637-4251.

Merial Limited
2100 Ronson Road
Iselin, NJ 08830-3077, U.S.A.

(Merial Limited: Registered in England and Wales [Reg. No. 3332751] with registered offices at 27 Knightsbridge, London, SW1X 7QT, England and domesticated in Delaware, USA as Merial LLC).

U.S. Pat. 4,199,569
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HEARTGARD™ Plus
box layout